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Adult Onset Drug Refractory Seizure Disorder Associated With Anti Voltage-Gated Potassium Channel Antibody

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Abstract

Voltage gated potassium channels are widely expressed throughout the entire nervous system. These channels play a critical role in establishing the resting membrane potential and generation of neuronal action potentials. There is mounting evidence that auto-antibodies reactive to neuronal cell surface antigens, such as voltage-gated potassium channels, play a pathogenic role in a wide spectrum of central and peripheral nervous system disorders. We report a case of new onset drug refractory seizure disorder associated with the presence of high levels of serum anti voltage-gated potassium channel antibodies that responded only to immunotherapy. As demonstrated by this case report, anti voltage-gated potassium channel antibody associated drug refractory seizure disorder, while rare, should be considered in patients with unexplained adult-onset seizure activity. Once the diagnosis has been established the initiation of immunotherapy should be undertaken without delay.

Keywords

VGKC antibody; Seizure Disorder; Limbic Encephalitis; Encephalopathy

INTRODUCTION

There is growing evidence that auto-antibodies reactive to neuronal cell surface antigens, such as voltage-gated potassium channels (VGKCs), play a pathogenic role in a wide spectrum of central and peripheral nervous system disorders. VGKCs are widely expressed throughout the entire nervous system and are critical in establishing the resting membrane potential and generation of neuronal action potentials. Studies of autoimmune limbic encephalitis (ALE) associated with anti-VGKC antibodies have shown a predilection to immunolabel the hippocampus and cerebellum (Vincent et al., 2004).

Recently several retrospective studies have shown an association between anti-VGKC antibodies and the development of new onset unexplained seizure disorder in patients with a constellation of ALE symptoms (Mcknight et al., 2005, Majoie et al., 2006). We report a

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patient presenting with new onset drug refractory seizure disorder associated with high levels of serum anti-VGKC channel antibodies that responded only to immunotherapy.

Case Report

A 64-year-old gentleman with no significant past medical history while traveling in South Africa developed gastroenteritis and myalgias. His symptoms resolved within a few days with hydration, however, he developed involuntary synchronous twitches of his right shoulder and occasionally face, occurring up to 30 times per minute. These symptoms were associated with occasional feelings of a “lump in the throat”, a “chill up the neck”, and disruption of train of thought. Four weeks later, after having returned to the United States and having stopped atovaquone/proguanil, taken for malaria prophylaxis, he experienced two witnessed episodes of sudden loss of consciousness (LOC), causing him to fall to the floor. He immediately regained consciousness with no clear postictal symptoms. Past medical and family history was unremarkable.

Physical examination revealed a healthy middle-aged white man with no carotid bruit or cardiac murmur. Mental status was alert and oriented, without aphasia. Neurological examination was normal. Brain MRI, three weeks after initial LOC, was interpreted as normal at another facility; however, upon retrospective review the left hippocampus and bilateral frontal lobes were felt to be hyperintense on FLAIR images with associated reduced diffusion of the frontal lobes (Figure 1). Subsequent EEG demonstrated multiple seizures lasting seconds to minutes, arising from the left anterior temporal lobe (Figure 2). The patient was started on oral levetiracetam 500 mg BID for complex partial seizures (CPS) because in our practice (D.C.E) we have found it provides protection against partial complex and generalized seizures with an improved side effect profile compared to alternative medication choices.

Over the next six weeks his CPS activity continued to progress; having up to 25 episodes per day despite titration of levetiracetam to 1500 mg BID, therefore, oral lamotrigine introduced 6 weeks after the initiation of symptoms and rapidly titrated up to 200 mg BID. Follow up brain MRI, two months after the start of seizure activity, was grossly abnormal with enlargement of the left greater than right hippocampus (Figure 3A–C) with increased bifrontal and medial temporal lobe hyperintensities on FLAIR images. Chest, abdomen, and pelvic CT scan showed no evidence of malignancy. A lumbar puncture revealed seven white blood cells (1% polys, 83% lymphs, 16% monos) with mildly elevated protein (56 mg/dL, normal 15–45 mg/dL) and negative cytology. IgG index and oligoclonal band analysis were not performed.

Four months after seizure onset, despite continued medical treatment, he continued to have multiple daily seizures and development of worsening short-term memory and emotional lability; crying and becoming angry. Due to clinical symptoms and abnormal MRI the diagnosis of anti-VGKC limbic encephalitis was considered. Serum was tested for anti-voltage-gated potassium-channel antibody levels, which were found to be elevated at 812 pmol/L (normal <150pmol/L; Athena Diagnostics, Inc. Worcester, MA).

Approximately five months after the first LOC episode all seizure activity ceased following the continued medical treatment with concurrent administration of prednisone 60 mg QOD and three courses of intravenous immunoglobulin (IVIg) 30 grams (0.4 grams/kg/day) daily for five days. Treatment with IVIg and prednisone was initiated because of worsening clinical symptoms concerning for limbic encephalitis in the setting of positive anti VGKC antibody levels. No validated treatment regiment currently exist for this disorder, however, the current literature advocates treatment directed at negating the presumed immune-

mediated etiology (Buckley et al., 2001; Geschwind, 2008; Hart, 2002; Pozo-Rosich, 2003; Thieben, 2004; Vincent, 2004; Urbach, 2006).

Over the next seven months he was maintained on lamotrigine and levetiracetam while being tapered off prednisone. Tapering of prednisone was done slowly because the patient had dramatically improved following its initiation, we did not want his symptoms to relapse, and we were unable to identify a standardized therapy regiment published in the literature to guide us in the tapering of this medication. Follow-up MRI of the brain ten months after clinical improvement following treatment with immunotherapy and fourteen month after the initiation of symptoms showed partial resolution of FLAIR hypertintensity (Figure 3D–F). Twenty four months following the sudden onset of seizure activity the patient remained clinically and electrographically seizure free. Due to the patient's significant clinical improvement and monetary concerns, we have not obtained repeat post-therapy VGKC antibody levels.

DISCUSSION

Epilepsy affects 1–2% of the general population; adult onset epilepsy, however, is relatively rare with an age adjusted incidence of 61 per 100,000 person-years (Ruggles et al., 2001). Several recent studies have identified patients with seizure activity associated with limbic encephalitis and anti-VGKC antibodies (Buckley et al., 2001; Geschwind et al., 2008; Graus et al., 2008; Hart et al., 2002; Thieben et al., 2004; Vincent et al., 2004; Tan et al., 2008; Tuzun et al., 2007; Vernino et al., 2007). Anti-VGKC antibody associated syndromes have a wide presenting spectrum ranging from a purely peripheral nervous system disorder manifested as Isaac's Syndrome to a purely central nervous system disorder manifested as adult onset drug refractory seizure disorder (Buckley et al., 2001; Josephs et al., 2004; Vincent et al., 2004; Tan et al., 2008; Tuzun & Dalmau, 2007; Vernino et al., 2007). In the case reported it is important to note that partial complex seizure activity was present for several months prior to the onset of behavioral changes and short-term memory dysfunction.

EEG in patients with anti-VGKC antibody associated seizure disorder often shows nonspecific abnormalities such as generalized background slowing, occasionally with superimposed unilateral or bilateral temporal slow waves and spike foci (Buckley et al., 2001; Hart et al., 2002; Pozo-Rosich et al., 2003; Thieben et al., 2004; Vincent et al., 2004; Tuzun & Dalmau, 2007; Vernino et al., 2007). Brain MRI is abnormal in most patients with anti-VGKC antibody associated seizure disorder (Buckley et al., 2001; Hart et al., 2002; Pozo-Rosich et al., 2003; Tan et al., 2008; Thieben et al., 2004; Vincent et al., 2004; Urbach et al., 2006). Medial temporal swelling and FLAIR hyperintensity is often observed within weeks or months of onset of seizure activity. Enhancement with gadolinium rarely occurs. Cortical DWI hyperintensity, often with restricted diffusion, as frequently occurs with seizures, is also found in anti-VGKC disorders, but resolves with cessation of seizures (Urbach et al., 2006). Follow up MRI several months after onset of symptoms can show continued FLAIR signal hyperintensity and hippocampal atrophy which often cannot be distinguished from hippocampal sclerosis (Urbach et al., 2006).

While no validated treatment protocols currently exist for anti-VGKC antibody associated seizure disorder, current treatment approaches are often directed at the presumed immune-mediated etiology. Published case series report a mixed response to treatment with plasma exchange (PE), IVIg, corticosteroids, cyclophosphamide, or tacrolimus (Buckley et al., 2001; Hart et al., 2002; Pozo-Rosich et al., 2003; Thieben et al., 2004; Vincent et al., 2004; Urbach et al., 2006). We have treated at least one patient with VGKC ALE and seizures who despite initial dramatic improvement with IV corticosteroids, later became refractory to PE, IVIg, mycophenolate mofetil, and IV corticosteroids, but responded to Rituximab

(Geschwind et al., 2008). The previously described mixed response to treatment may be due to the progressive course being pathologically associated with astrocytic gliosis, neuronal atrophy, and eventually neuronal death, thus making full recovery from clinical symptoms impossible. A case series of ten anti-VGKC antibody associated ALE and seizure disorder treated with a 5-day course of plasma exchange, 0.4 mg/kg/day of IVIg, or both, followed by a course of oral corticosteroids reported improved memory function in nine of ten patients, however, ongoing selective memory impairment remained (Vincent et al., 2004).

In our patient, clues to diagnosis of anti-VGKC mediated seizure disorder were 1.) the initial right sided simultaneous brief spasms of the arm and face, 2.) adult-onset seizure disorder refractory to multiple AEDs, 3.) brain MRI showing medial temporal lobe hyperintensity with possible cortical gyral hyperintensity and 4.) the development of behavioral and personality changes. Unlike the majority of patients with VGKC ALE who develop hyponatremia (presumed syndrome of inappropriate antidiuretic hormone) (Geschwind et al., 2008), this was not present in our patient. Involuntary movements are commonly seen in anti-VGKC disorders. Sometimes these are associated with brief lapses of consciousness or “loss of train of thought,” although many times there is no change in consciousness and the patient is quite aware of these movements. . It is not clear if the latter are seizures or a movement disorder. A search for malignancy was performed in this case as VGKC antibody associated syndromes can occur with occult tumors, however, a majority of ALE cases are of non-paraneoplastic origin (Geschwind et al., 2008; Graus et al., 2008; Tan et al. 2008). When anti-VGKC antibodies are identified in the setting of a neurological disorder, immunosuppressive therapy should not be delayed while a search for primary malignancy is undertaken because the potential for permanent neurological damage is significant (Tuzun & Dalmau, 2007; Vernino et al., 2007).

CONCLUSION

As demonstrated by our case report, anti-VGKC antibody-associated seizure disorder, while rare, can present as new onset adult temporal lobe epilepsy. This etiology should be considered in any patient with unexplained adult-onset seizure activity, including temporal lobe epilepsy, as it is a treatable disorder. If suspected, serum antibodies should be sent and a search for primary malignancy should be performed. Once the diagnosis of anti-VGKC antibody associated seizure activity has been established the initiation of immunotherapy should be undertaken without delay.

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Figure 1.

MR imaging of the medial temporal and frontal lobes of the brain three weeks after onset of seizure activity. A–C) Coronal FLAIR, axial FLAIR, and diffusion images demonstrates hyperintensity within the left hippocampus (arrows) without associated reduced diffusion. D–E) Axial FLAIR and diffusion images demonstrate hyperintensity within the bilateral frontal lobes with associated reduced diffusion (arrows).

Figure 2. EEG three weeks after initiation of seizure activity demonstrates complex partial seizure activity in the left temporal lobes with slowing in the left frontal regions.

Figure 3.

Pre and post immunotherapy follow up MR imaging. A–C) Pre immunotherapy follow up coronal and axial FLAIR MR imaging eight weeks after initiation of seizure activity shows progression (from the initial MRI at three weeks) of hyperintensity and swelling within the left hippocampus (arrow), bilateral medial temporal lobes (arrow), and bilateral frontal lobes (arrow). D–F) Follow up coronal FLAIR and axial T2 fast spin echo MR images seven weeks after initiation of immunotherapy demonstrates improvement of hyperintensities within the hippocampus, medial temporal, and frontal lobes. Reduction of T2 hyperintensity may be most noticeable by comparing image B to E. Unfortunately, an axial FLAIR sequence was not acquired on post-immunotherapy follow-up MRI.